

Neurocognitive Effects of Chemotherapy

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Neurocognitive Research Lab

Memorial Sloan-Kettering Cancer Center

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Collaborators

- Andrew Saykin
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- Marie Bakitas

Interdisciplinary Team

- Neuropsychology
- Neuropsychiatry
- Oncology
- Hematology
- Neurology
- Neuroimaging
- Molecular Genetics
- Neuropathology
- Pharmacology
- Immunology
- Endocrinology
- Cognitive Rehabilitation
- Animal Learning Models
- Genetic Informatics
- Biostatistics

Cognitive Impact of Cancer Therapies

- Cranial radiation +/- intrathecal chemo
- Cranial surgery
- Biological response modifiers
- High-dose chemotherapy
- Standard-dose chemotherapy
- Hormonal Therapies

Importance of Studying Cognitive Decline Secondary to Cancer Therapy

- A challenge facing cancer survivors as identified by the National Coalition for Cancer Survivorship
- Negative impact on work/school performance and QOL
- Informed decision-making
- Similar pediatric research resulted in treatment modifications that reduced negative cognitive effects while maintaining treatment efficacy
- Development of interventions to prevent or treat cognitive decline

Common Cognitive Problems Reported Post-Treatment

- Memory and Concentration
- Executive Function
- Ability to Learn New Material /Reading Comprehension
- Ability to Work with Numbers

Pattern of Cognitive Problems

- Not everyone is affected (15-20%)
- Problems may come and go (Good and bad days)
- Often worse when:
 - Multitasking
 - Under stress or deadline pressure
 - Tired

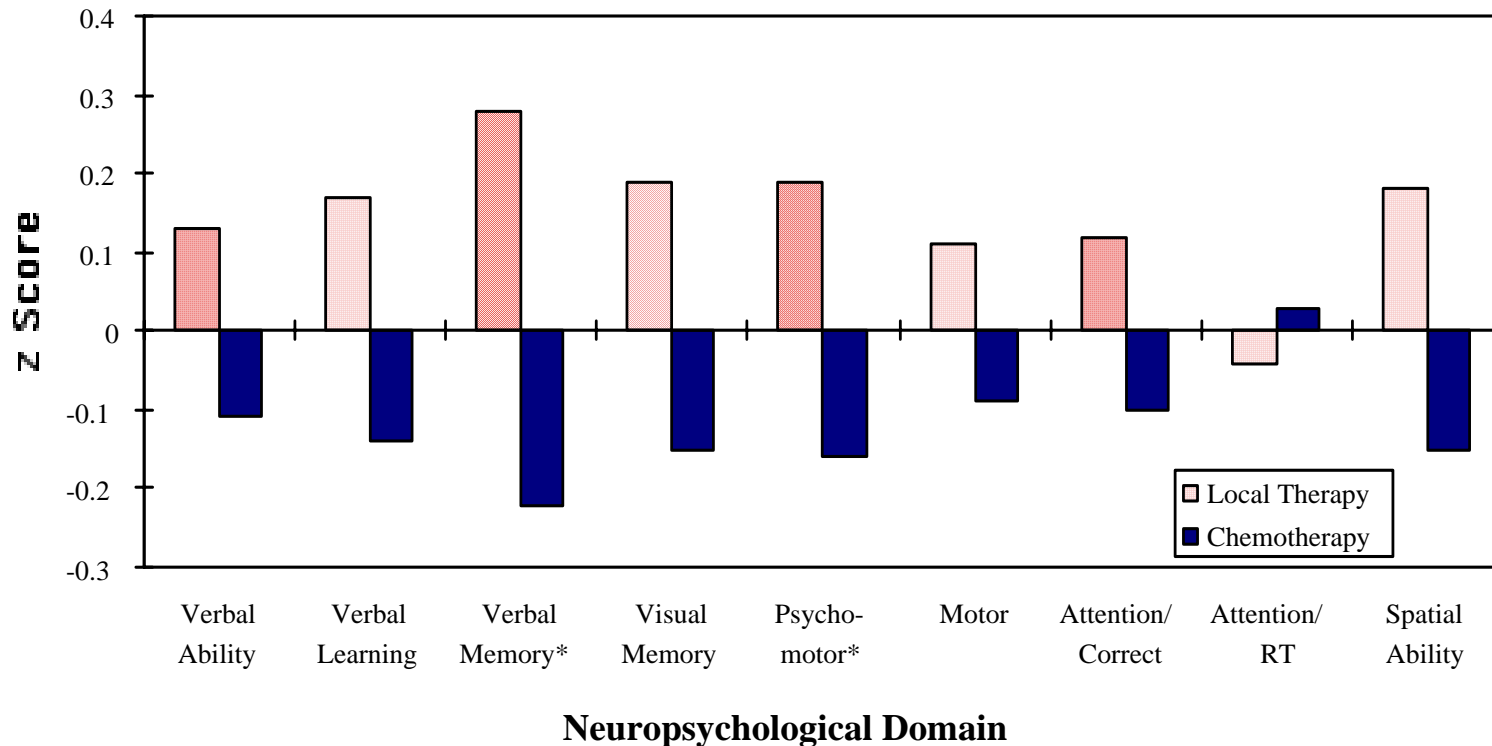
Factors Affecting Cognitive Functioning

- Fatigue
- Depression, anxiety, stress
- Pain and pain medications
- Other physical illnesses

Results of Post-treatment Studies

- Poorer cognitive performance for survivors treated with chemotherapy evaluated 6 months to 10 years post-treatment compared to survivors not exposed to chemotherapy
- Only a subgroup of survivors (17-35%) experienced persistent cognitive problems
- Cognitive problems not explained by depression, anxiety, or fatigue

Adjusted z-Transformed Domain Scores for the Chemotherapy vs. Local Therapy Groups



*p<.05, adjusted for age and education

First Meeting of the International Cancer and Cognition Working Group: Banff, Canada, April, 2003

- A group of 30 researchers shared results of ongoing studies and discussed future directions
- Emphasized the importance of conducting longitudinal studies

Longitudinal Assessment of Cognitive Functioning

- Importance of pretreatment assessments
- Importance of appropriate controls given the same test battery over similar time frames to control for practice effects

Second Meeting of the International Cancer and Cognition Working Group: Venice Italy, October, 2006

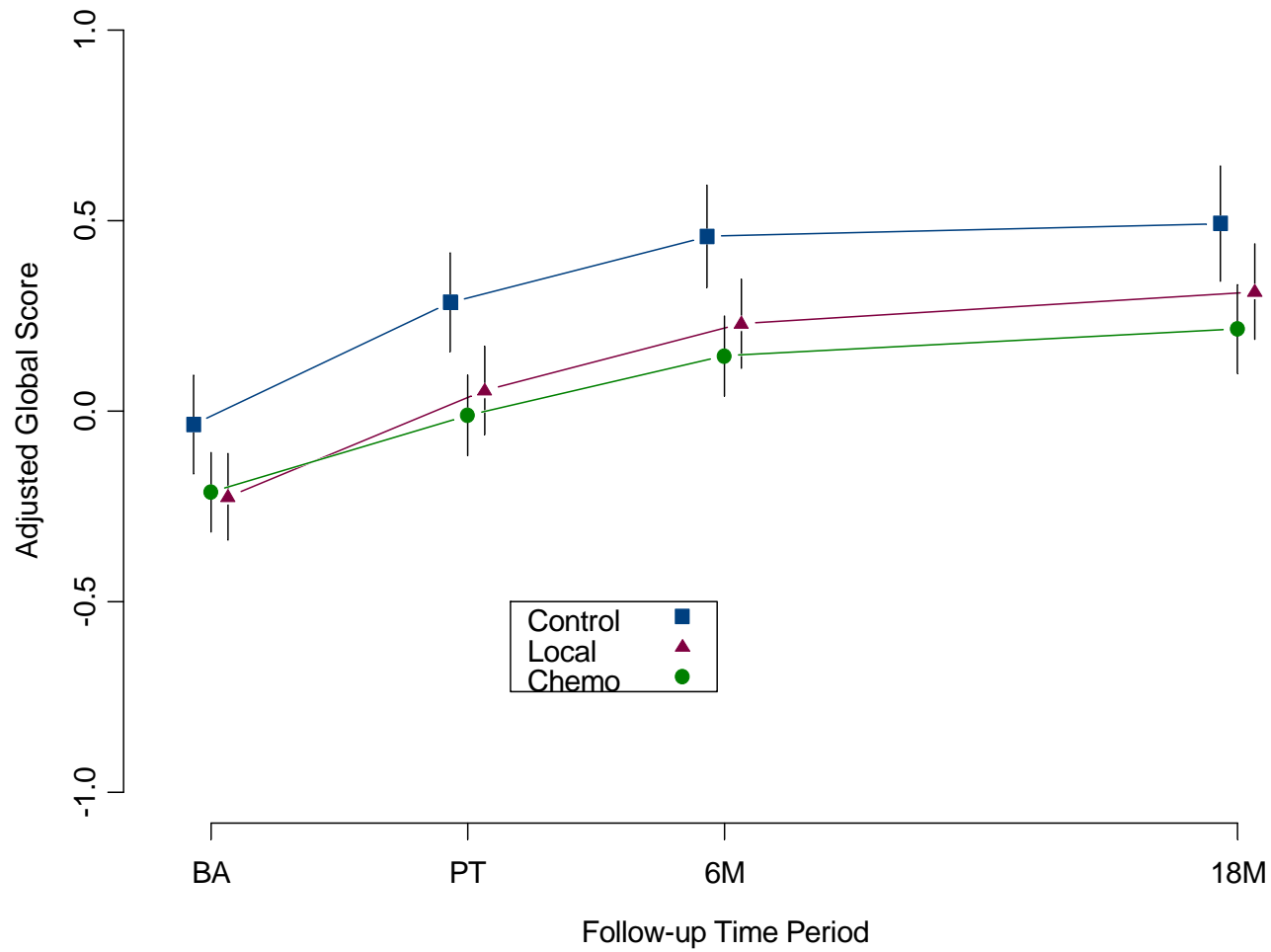
- Slightly larger group of researchers (50) shared results of longitudinal studies using neuropsychological measures
- Formed the International Cognition and Cancer Task Force
 - Steering Committee: Janette Vardy, MD, Sanne Schagen, PhD, Jeffery Wefel, PhD, Tim Ahles, PhD

Results of Longitudinal Studies

- 20-30% of breast cancer patients demonstrate lower than expected cognitive performance prior to adjuvant treatment
- Patients treated with chemotherapy and patients treated with non-chemotherapy-based regimens performed more poorly than matched healthy controls

Global

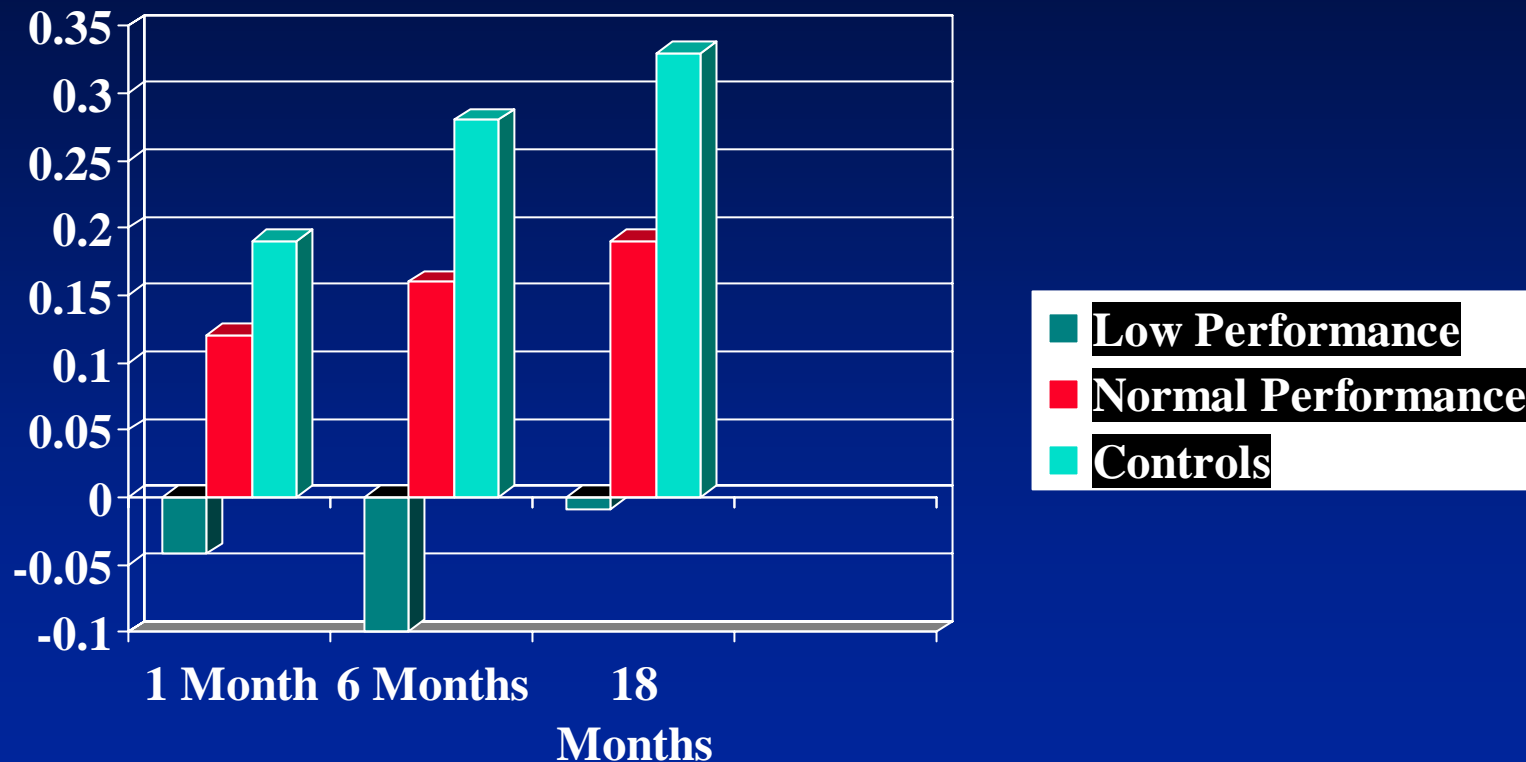
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Pretreatment Cognitive Performance?

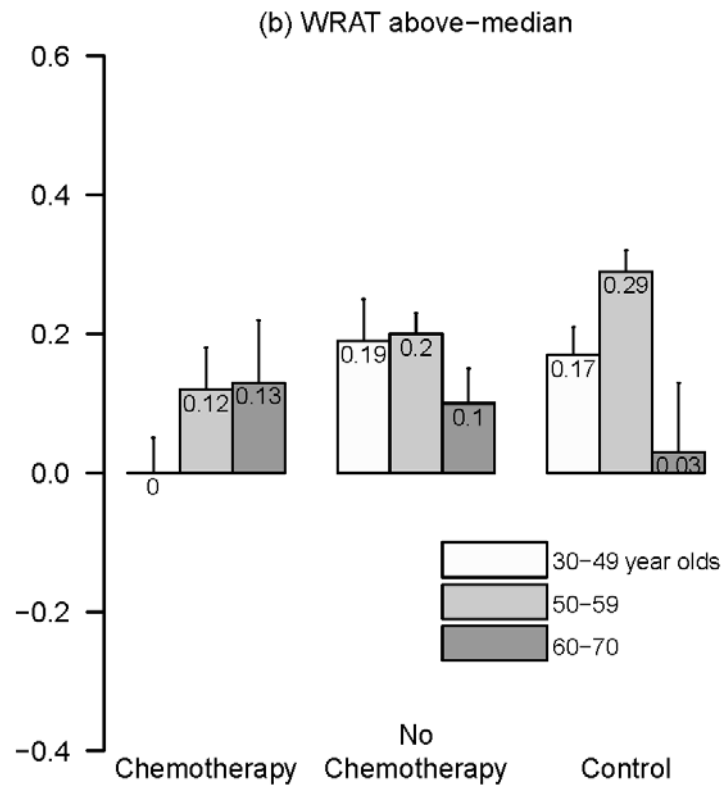
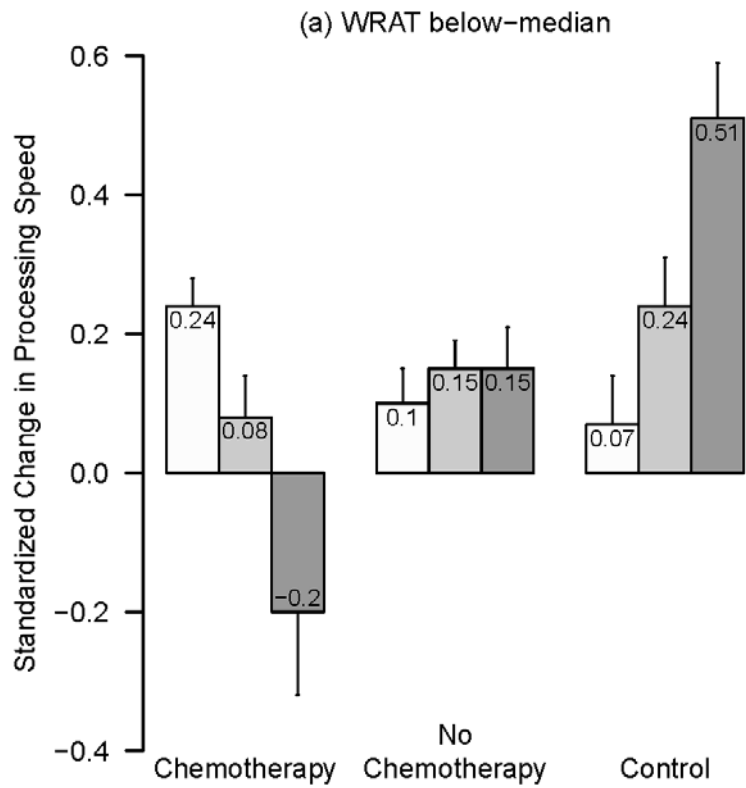
- Compared pretreatment neuropsychological assessment of breast cancer patients (N=132) to matched, healthy controls (N=45)
- Healthy controls (4%), Stage 0 (0%), Stage 1-3 (22%), $p < 0.02$ based on testing
- No differences among groups in self-reported cognitive problems
- Other groups reporting rates of lower than expected cognitive performance from 25-35%

Processing Speed: Change Scores from Baseline



Cognitive Reserve

- Innate and developed cognitive capacity
- Influenced by genetics, education, occupational attainment, life-style
- Higher cognitive reserve has been associated with less change in cognitive functioning following a brain insult or with normal aging



Potential Explanations for Pretreatment Differences

- Shared risk factors for development of cancer and mild cognitive decline
- Potential role of DNA damage and the genetics of DNA repair

DNA Damage and Cognition

- DNA damage is linked to both risk for cancer and neurodegenerative diseases like Alzheimer's disease and Parkinson's disease
- Patients with mild cognitive impairment have higher levels of DNA damage
- Patients with cancer have higher levels of DNA damage at diagnosis

DNA Damage and Cognition

- Chemotherapy causes DNA damage
- Working Hypothesis: DNA damage may be related to cognitive functioning both pre- and post-chemotherapy

Pre-Cancer Diagnosis

Cancer Treatments

DNA Repair Genes

Endogenous
Oxidative
Stress

Genotoxic Exposures

DNA Damage

Chemotherapy

Radiation
Therapy

Endocrine
Therapy

Decreased Cognitive
Function

Memorial Studies Examining the Relationship between Cognition and DNA Damage-Survivor Study

- Breast cancer survivors 3-6 years post treatment with endocrine therapy plus or minus chemotherapy and matched healthy controls
- Neuropsychological Assessment
- DNA Damage-Comet Assay

Memorial Studies Examining the Relationship between Cognition and DNA Damage- Longitudinal Study

- Breast cancer patients treated with AC-T or no chemotherapy and healthy controls
- Assessed pre- and post-treatment
- Neuropsychological Assessment
- Structural and Functional MRI
- DNA damage-Comet Assay

Factors Influencing Post-Treatment Results

- Potential role of endocrine treatments (Tamoxifen and Aromatase Inhibitors)
- Role of chemotherapy-induced menopause
- Estrogen reduction may be associated with cognitive change

Renaming “Chemobrain”

- Cancer or cancer-associated cognitive change
- “if you have Tim's e-mail address, maybe contact him and say if he expects his favorite project to resonate with the general public, he'd better leave the name as is because "chemobrain" slips off the tongue quite willingly, while the proposed new name is a gnarly mouthful!”

Neuropsychological Testing

- Primarily designed to assess people with significant brain damage (stroke, head injury) or disease (Alzheimer's)
- Problem: Many cancer survivors score well within the normal range even though they report having cognitive problems

Results of MRI, PET and EEG Studies

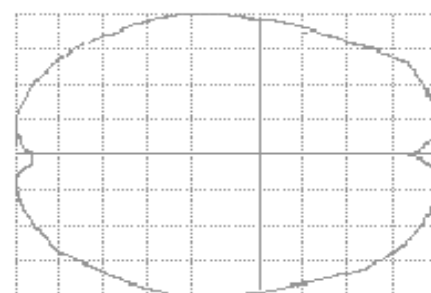
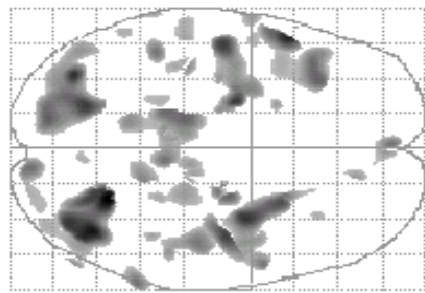
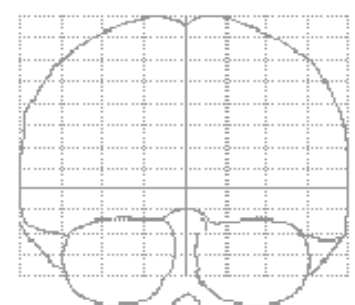
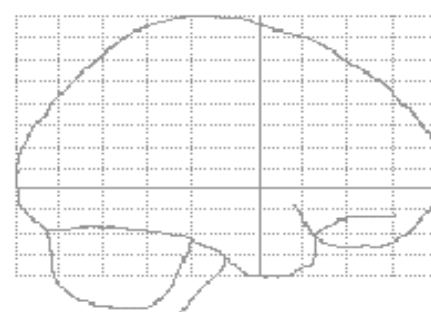
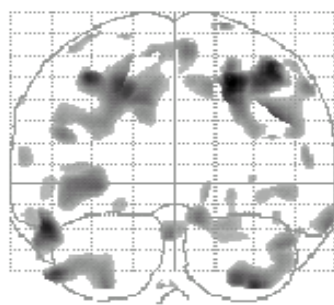
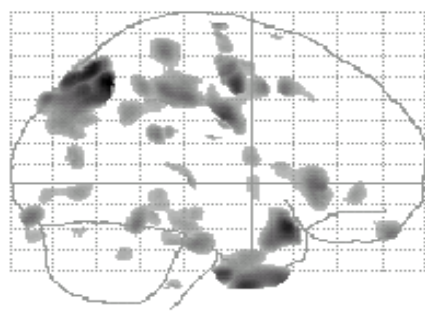
- MRI and PET studies suggest that there are changes in brain structure and function associated with chemotherapy
- EEG studies suggest changes in measures of information processing (P300) associated with chemotherapy

Regions of Local Gray Matter Volume Reduction in Chemotherapy Treated Cancer Survivors Compared to Healthy Controls on Voxel Based Morphometry

Controls > Chemotherapy Chemotherapy > Controls

L

R



Patients (n=12)
Controls (n=12)

$p < .01, k=24$

Regions of Local White Matter Volume Reduction in Chemotherapy Treated Cancer Survivors Compared to Healthy Controls on Voxel Based Morphometry

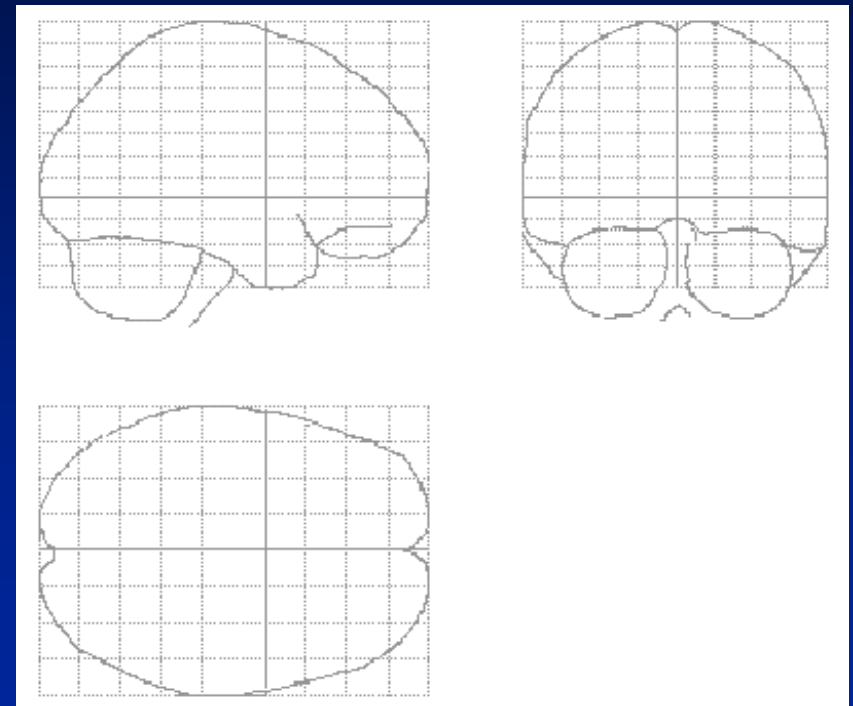
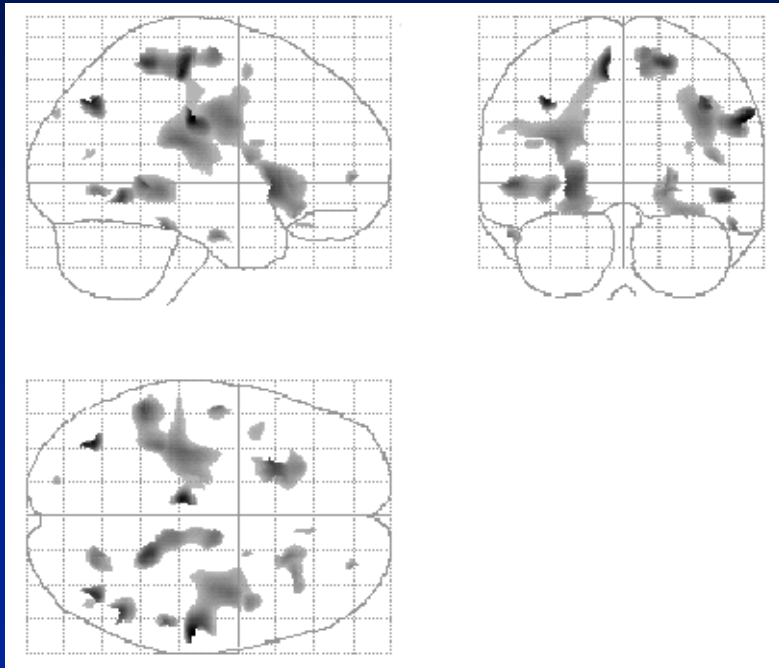
Controls > Chemotherapy

L

R

Chemotherapy >

Controls



Patients (n=12)
Controls (n=12)

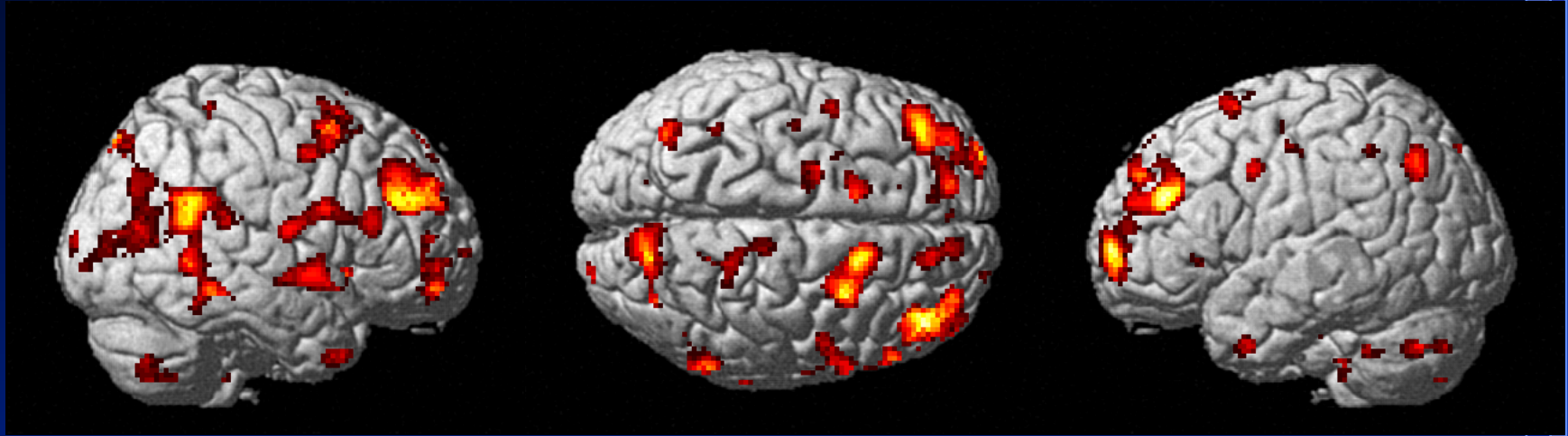
$p < .01, k=24$

Fig 2: Decreased working memory fMRI activation and gray matter density from baseline to 1 month post chemotherapy

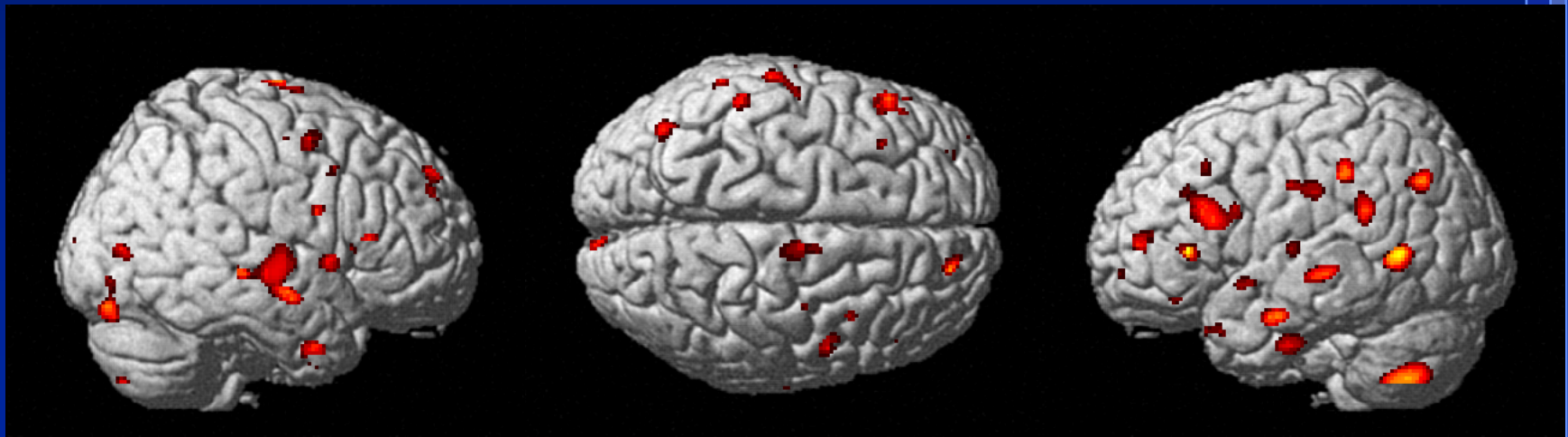
Right

Left

Working Memory



GM Density



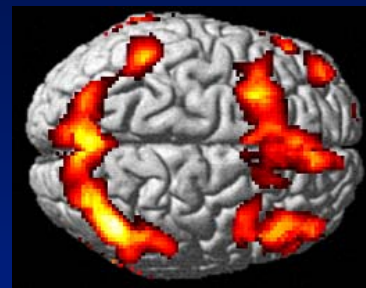
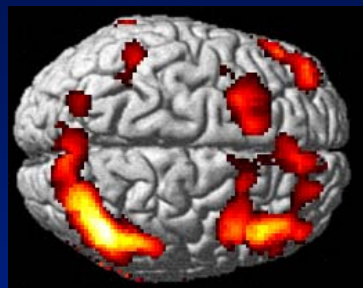
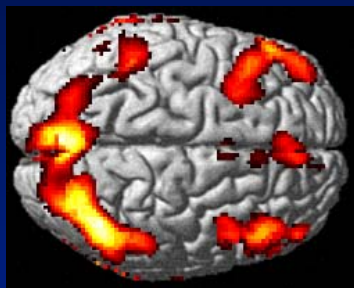
Contrast: Chemo Tx (n=17) vs. Local Tx (n=7) & Healthy Controls (n=9) $p < .01$

fMRI Activation Pattern for Identical Twins Discordant for Breast Cancer

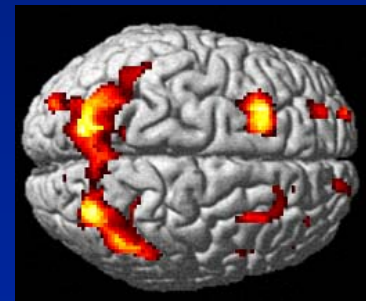
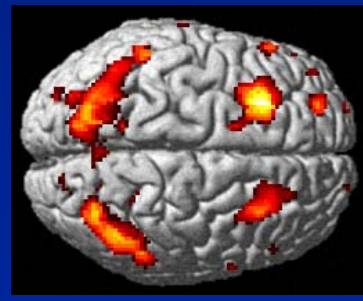
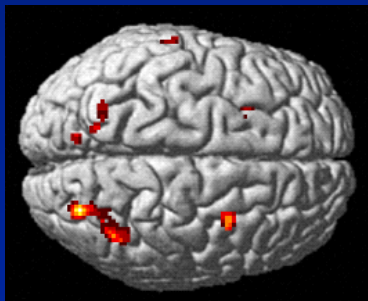
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2-back>0-back

3-back>0-back



Chemotherapy-treated Twin-Twin A



Non-cancer Twin-Twin B

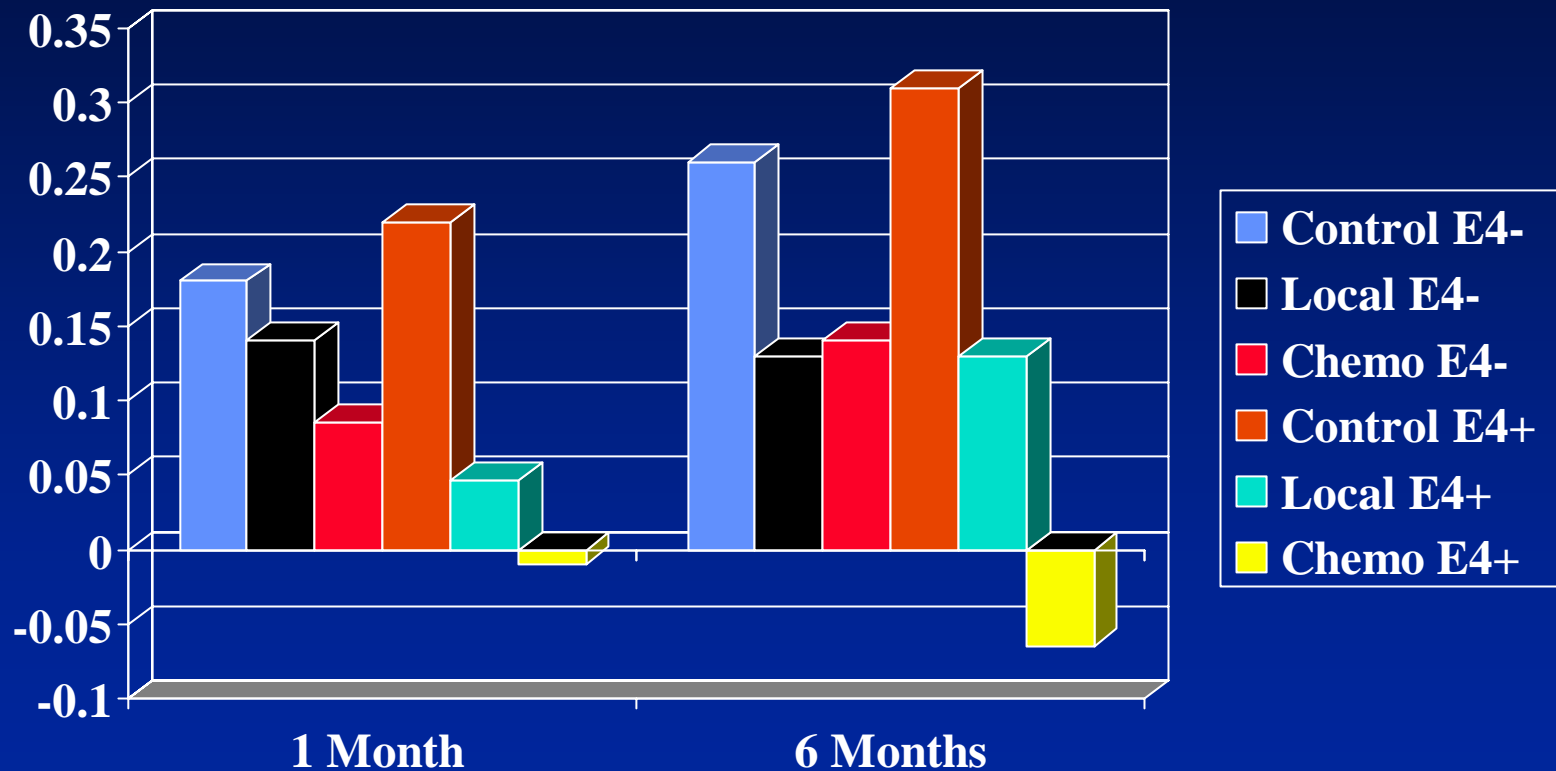
Future Directions

- Traditional neuropsychological tests may not be sensitive to subtle changes associated with chemotherapy because patients can compensate by activating alternative brain structures
- May need to partner with cognitive psychologists to develop tasks that push cognitive capacity
- May need to incorporate these tasks into imaging and EEG studies

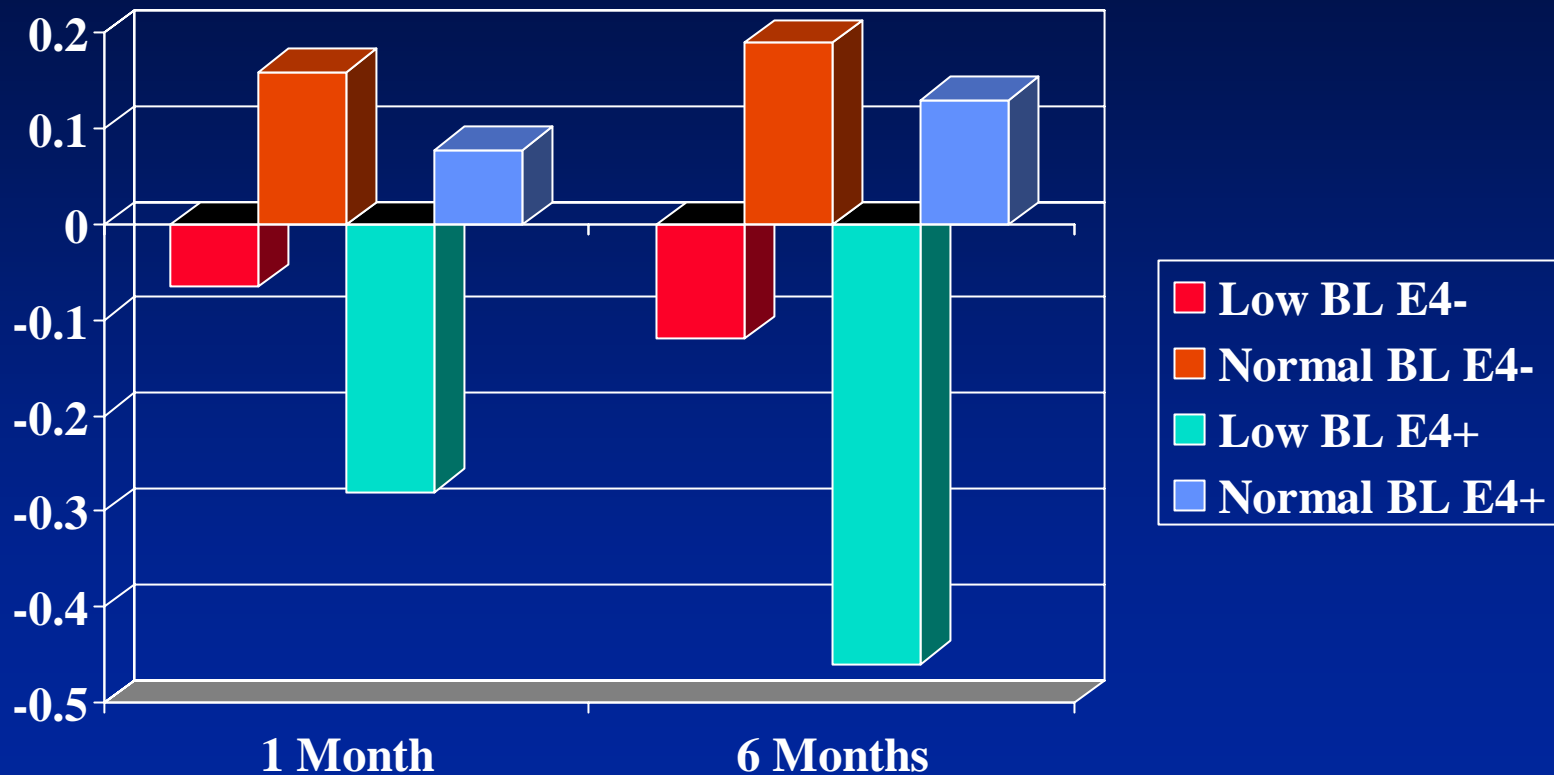
Genetic Factors

- Repair of nerves and blood vessels (APOE)
 - DNA repair
 - Inflammatory response
 - Blood brain barrier
-
- Understanding genetic risk factors may lead to tailored treatments which avoid toxicities like cognitive problems

Processing Speed Change from Baseline: Group by APOE



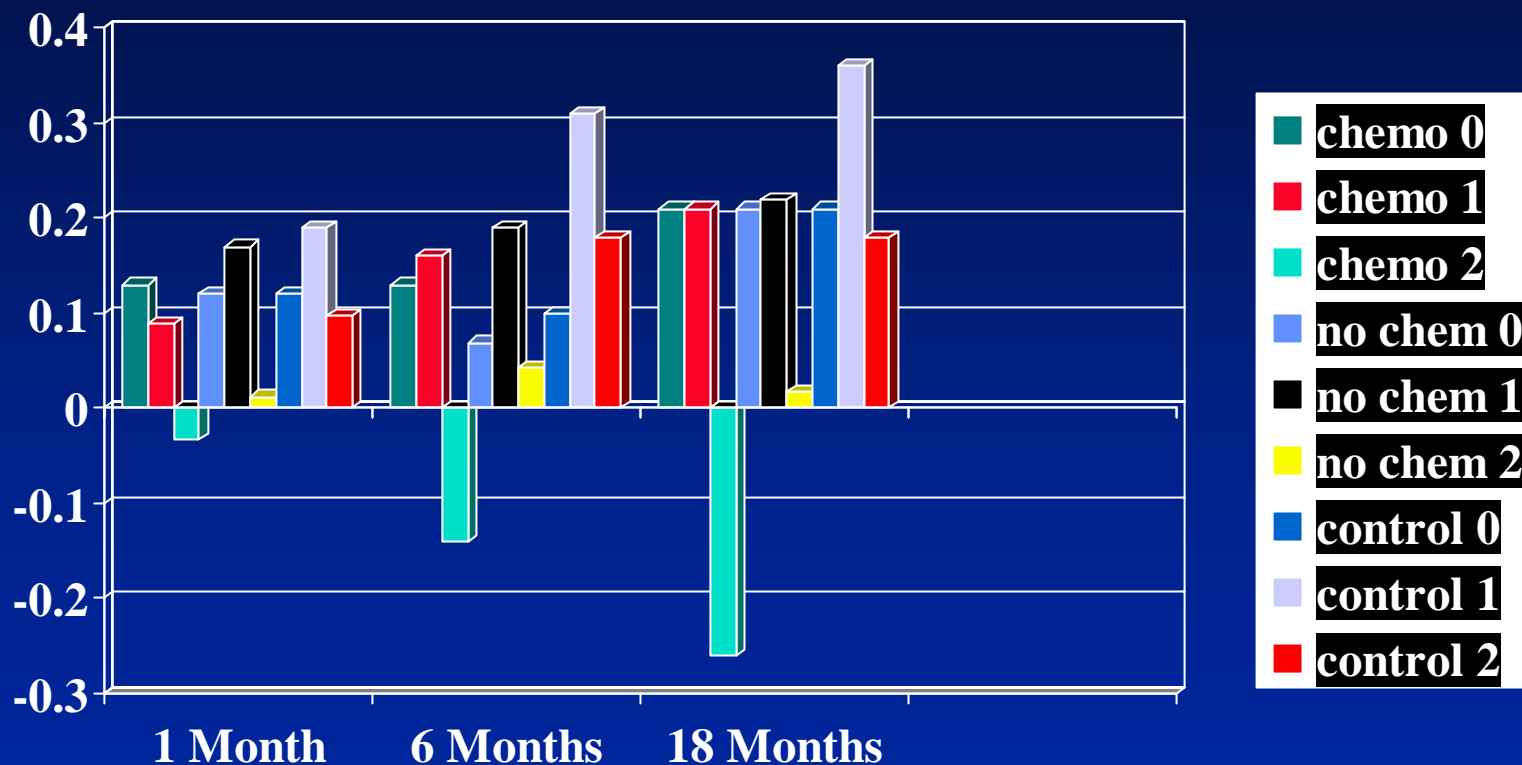
Processing Speed Change from Baseline: Baseline Impairment by APOE



Potential Mechanisms

- Reduction in microvascular or neuronal repair processes associated with the APOE - ϵ 4 allele
- Pre-existing morphologic differences (e.g., smaller hippocampal volume) associated with the APOE - ϵ 4 allele

Processing Speed: Change Scores from Baseline: MRE11A (472344)



Telomere Length, Cancer and Cognition

- Telomeres are DNA-protein complexes that cap the end of chromosomes and promote stability
- Telomeres shorten with replication eventually leading to cell senescence and cell death
- Telomere shortening is associated with aging, cancer predisposition and Alzheimer's disease

Chemotherapy and Accelerated Ageing

- Many common chemotherapy agents cause shortening of telomeres
- Working Hypothesis: Chemotherapy may have a long-term effect on cognitive function by shortening telomeres

Animal Studies

- Deficits on learning and memory tasks following administration of chemotherapy
- Disruption of hippocampal neurogenesis even at doses that are ineffective for killing cancer cells
- Acute and delayed damage to white matter tracks associated with 5-FU

Future Animal Studies

- Impact of chemotherapy on hippocampal neurogenesis (Daniel Herrera, Harvard)
- Impact of chemotherapy on cell senescence (Karen Hubbard, City College)

Interventions

- Pharmacologic Interventions
 - psychostimulants
 - cholinesterase inhibitors
 - gingko biloba
- Cognitive Rehabilitation



NORRIS COTTON CANCER CENTER
DARTMOUTH-HITCHCOCK MEDICAL CENTER

Memory and Attention Training:

A Brief Behavioral Skills Program for Cancer Survivors with Attention and Memory Problems Associated with Chemotherapy

Robert J. Ferguson, Ph.D.*

Behavioral Medicine Section

Dartmouth Medical School

RUNNING HEAD: Memory and Attention Training

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Memory and Attention Training

- Education
 - Common cognitive errors
 - Different types of memory and attention

Memory and Attention Training

- Compensatory Strategies
 - Lists, calendars, palm pilots
 - Self-instructional training
 - Scheduling / Time management
 - Sleep hygiene / Fatigue management

Memory and Attention Training

- Relaxation Training
 - Progressive Muscle Relaxation
 - Breathing exercises

Memory and Attention Training

- Problem-Solving
 - A structured approach to applying the skills in everyday life

Summary

- Cognitive problems experienced by cancer patients are likely not exclusively associated with chemotherapy
- Pretreatment cognitive problems suggest that there may be common risk factors for development of cancer and cognitive problems
- Imaging techniques will be important to understanding cognitive changes associated with breast cancer treatments
- Genetic factors are likely important in increasing vulnerability for long-term cognitive problems
- Medication and cognitive rehabilitation interventions are being evaluated



Save the Date:



ICCTF COGNITIVE SYMPOSIA



March 8-9, 2010
(Monday/Tuesday)

Memorial Sloan-Kettering
Cancer Center
New York, NY

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CANCER TASK FORCE (ICCTF): www.icctf.com